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USE OF PROCAINE AMIDE IN CARDIAC ARRHYTHMIAS

The antiarrhythmic properties of procaine were first utilized during pericardial surgery by Beck and Mautz in 1936[1]. These surgeons applied the drug topically to the heart and observed a decreased incidence of cardiac arrhythmias. The intravenous administration of procaine was introduced by Burstein[2] for its antiarrhythmic action and during the last 10 years it has been widely employed by anesthetists during surgical procedures, especially in cardiac and thoracic operations. The drug's stimulatory action on the central nervous system, has, however, limited its use to the anesthetized patient. In addition, the antiarrhythmic action is transient because of the exceedingly rapid hydrolysis of procaine in the blood stream to *p*-aminobenzoic acid and diethylaminoethanol. The latter compound retains the antiarrhythmic properties of procaine to some degree and may have limited usefulness, though very large doses are required for an effect[3].

Search for a better antiarrhythmic agent led to the synthesis of a number of derivatives of diethylaminoethanol which were screened for their antiarrhythmic action, using as a test the prevention of epinephrine-induced ventricular tachycardia in dogs under cyclopropane anesthesia[4]. The most satisfactory compound found for protecting dogs against the induced arrhythmias was procaine amide, the amide analogue of procaine[5]. Further studies in man showed that the drug does not produce central nervous system stimulation in therapeutic doses and that it is unaffected by the enzyme responsible for the rapid hydrolysis of procaine. Gastrointestinal absorption was found to be rapid and complete, peak levels being obtained at about 90 minutes after an oral dose. The drug is slowly metabolized and excreted, plasma levels declining approximately 15% an hour. A considerable proportion is excreted unchanged by the kidneys. On repeated oral dosage the plasma levels reach a relative plateau after 36 — 48 hours[5].

The clinical use of procaine amide in various cardiac arrhythmias was then studied[6]. Recurrent premature ventricular contractions were treated in a group of 55 patients. The premature beats were attributable in some instances to excessive digitalis, in others they were associated with organic heart disease, mostly arteriosclerotic in nature. In all instances, the drug, administered either orally or intravenously in doses of 0.4 to 1.0 gram suppressed the ectopic beats, though the period of suppression varied from a few minutes to many hours. The usual length of the period of suppression after a single intravenous dose was from three to six hours. In 25 of 40 patients given the drug intravenously, the period of suppression fell within this range. Suppression of extrasystoles on intravenous administration occurred during or shortly following the period of injection; after oral administration there was usually a delay of an hour. Continued oral administration of the drug in 15 patients for several months successfully prevented the recurrence of the extrasystoles.

The most important use of procaine amide was, however, shown to be in the control of ventricular tachycardias. The drug was administered to 16 patients with ventricular tachycardia, eight of whom were suffering from acute myocardial infarction. In 14 of them, the administration of the drug orally, intravenously, or by both routes, was successful in terminating the aberrant rhythm and restoring the supraventricular pacemaker. In two patients, the drug failed to abolish the ventricular tachycardia. Attention should be drawn to the fact that seven of the 14 patients had previously been treated with quinidine to toxicity without altering the rhythm. It is evident from this experience and that cited above that the presence of large amounts of digitalis or quinidine in the body does not contraindicate the use of procaine amide.

Supraventricular arrhythmias were then studied in 28 patients. The effect of procaine amide in this group has been much less spectacular and evidently requires further study. The intravenous administration of 1.0 gram to 14 patients with chronic auricular fibrillation and 10 patients with chronic auricular flutter failed to alter the rhythm although an effect on auricular activity was observed in that there was marked slowing of the rate of the F' waves. Four patients with recently established auricular fibrillation (three days to a week) have responded with the appearance of normal sinus rhythm during the intravenous administration of procaine amide. Several reports have recently been received which indicate that recent auricular fibrillation is also susceptible to *orally* administered procaine amide. Two patients with nodal tachycardia were treated with the drug. One reverted to normal sinus rhythm once on oral administration and twice on intravenous injection; the other did not respond. The duration of the abnormal rhythm appears from this limited experience to be of great importance.

At first the drug was given intravenously in order to assess its action accurately. On the basis of animal experiments and preliminary investigations in humans, the rate of intravenous administration was arbitrarily set at 200 mgm. a minute until the aberrant rhythm had been interrupted or a total of 1.0 gram had been administered. Transient moderate hypotension was observed in about one-third of patients who did not have tachycardia. In patients with ventricular tachycardia, in whom hypotension

was already present, intravenous administration caused a further depression which disappeared promptly with the establishment of a supraventricular rhythm.

Other investigators have confirmed the effectiveness of the drug in ventricular arrhythmias, but have observed a greater degree of hypotension on intravenous injection to patients with cardiac arrhythmias[7, 8]. Stearns, Calahan, and Ellis[7] have noted significant hypotension on total doses ranging from 70 to 800 mgm. even when the rate of injection was reduced to 25 — 100 mgm. a minute. They observed also that the total dose required for terminating an attack of ventricular tachycardia was less than 500 mgm. in five of six patients. Bellet, Garlett, and Berry[8] have also reported the development of marked hypotension on intravenous use of procaine amide. In addition, they believed that the peak effect occurred about four minutes after intravenous injection.

In studying the use of procaine amide two facts quickly became apparent: one, that oral administration was effective, and two, that hypotension did not develop on oral administration. The oral route obviously, therefore, became the preferred one except for those patients who were critically ill or unable to take oral medication. Under these circumstances intravenous therapy remains a necessity though the rate of administration in the light of the experience of the other groups[7, 8] might well be slower than that employed in our studies. The danger of too rapid administration needs emphasis. Early in our series one patient died not from hypotension, but with the development of ventricular fibrillation which, in retrospect, was thought due to too rapid administration of the drug. An injection of 100 mgm. a minute or even less until the desired effect is achieved, or a total of 1.0 gram administered may prove to be safer and just as effective as the more rapid rate. The effective oral dose for patients with ventricular tachycardia varies widely. An initial dose of 1.25 grams followed in one hour by an additional 0.75 grams, if the tachycardia persists, has been successful in the majority of our patients. If this dose is not effective, subsequent doses of 0.5 to 1.0 gram every two hours may eliminate the aberrant rhythm. Oral therapy often had to be maintained for long periods of time to prevent recurrence of either extrasystoles or paroxysms of ventricular tachycardia. The effective dosage for maintainence therapy ranged from 0.5 to 1.0 gram every three to six hours. One or two individuals have received the drug continually for as long as nine months without apparent harmful effect.

Toxic effects have been limited to the gastrointestinal and circulatory systems. Anorexia, nausea, and vomiting were observed on high oral therapeutic schedules (6.0 to 8.0 grams a day). Transient electrocardiographic changes are seen in about one-third of patients receiving a single dose and these may persist in patients on prolonged oral treatment. These changes consist in widening of QRS and QT intervals and decreases in amplitude of QRS and T waves. As previously discussed, the intravenous administration of procaine amide to patients with cardiac arrhythmias may cause or accentuate hypotension. It has been suggested that a vasopressor drug (neosynephrine) be quickly administered to combat the hypotension[7]. In our experience hypotension has rarely appeared to be serious enough to warrant therapy. The theoretical objection that vasopressor drugs may induce other cardiac arrhythmias must, however, be borne in mind.

Procaine amide is also useful in the treatment of cardiac arrhythmias arising during surgical anesthesia. A dose of 300 to 600 mgm. injected slowly to minimize hypotensive effects has suppressed the majority of abnormal rhythms. Studies of the prophylactic action of procaine amide against the occurrence of arrhythmias during intrathoracic surgery have yielded promising results[9]. A dose of 1.0 gram by mouth was given one hour before operation, and a second gram was given intravenously in divided doses during the period from the skin incision to the moment of entry into the chest. In comparison to the control series, the incidence of cardiac arrhythmias was decreased by one-half, and that of ventricular arrhythmias by two-thirds. Procaine amide given in the course of procedures employing cardiac catheterization has likewise frequently failed to abolish or prevent ectopic beats[10]. That the ventricular arrhythmias were unaffected in many instances suggests that some mechanical stimuli may be too great to be inhibited by the drug.

Summary

1. Procaine amide (Pronestyl Hydrochloride*) is an effective drug for stopping ventricular tachycardias and ventricular premature contractions.

2. Some evidence is accumulating to suggest that it may be effective in recent auricular arrhythmias. It appears to be ineffective in abolishing auricular fibrillation or flutter of long standing.

3. The drug should be given by mouth whenever possible. If the necessity for intravenous administration arises it should be given slowly (100 mgm/min or even less).

4. The presence of large amounts of either digitalis or quinidine in the body does not contraindicate its use.

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*Supplied by E. R. Squibb & Co.

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